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NH insertion reactions catalyzed by reusable water-soluble ruthenium (II)-*hm*-phenyloxazoline complex

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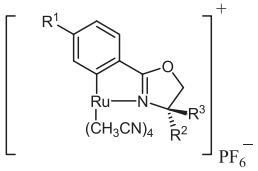
ABSTRACT

A water-soluble Ru(II)-*hm*-pheox complex was efficiently catalyzed NH insertion of EDA with a broad class of amine derivatives in water/ether biphasic medium to deliver the biologically active precursors α-aminoester products with excellent yields (up to >99%). The products were separated by decantation and the catalyst was washed and reused several times (at least 8 times) without any specific loss of its catalytic activity. The plausible mechanism of the reaction was explained. Additionally, In case of ethylene diamine, the NH insertion product could be transformed to biological active piperazinone compound in high yield. The asymmetric version of this catalytic reaction is under investigation.

The N–H insertion of diazo-compounds into primary or secondary amines have great benefits for formation of different α-amino esters, peptide synthesis,[1] medicinal chemistry,[2,3] and as precursors for a wide variety of biologically active compounds, pharmaceuticals,[4] and natural products.[5] Despite the efforts devoted in this reaction from the pionering work using copper bronze[6] and the subsequent catalysts to date,[7] The potent and reusable catalyst still remain a challenge. Especially, the water-soluble and reusable catalyst is of great interest as a type of green catalytic chemistry. And because of the low solubility of most of the organic compounds in water beside the sensitivity of some organic compounds and intermediates to water, most of the researchers avoided using water in organic reactions as a solvent. In 2014, J. Akbari et al. reported the use of acidic ionic liquid [Hmim][BF_4] for EDA insertion into amines,[8] Water/CH_2Cl_2 were added at the end of reaction to separate the product in CH_2Cl_2 by decanting the organic layer and recovering the catalyst in water. Neverthless the substrate scope was limited and the reusability was unclear. Recently, we reported the successful use of the novel water-soluble chiral Ru(II)-*hm*-Pheox catalyst **1** in intramolecular cyclopropanation of *trans*-allylic diazoacetates and alkenyl diazoketones that afforded excellent enantioselectivities and yields and the catalyst could be reused five times.[9] Encouraged by this results, we selected the NH-insertion reaction as one of the carbene insertion reaction to evaluate the catalytic activity of our non-chiral water-soluble catalyst Ru(II)-*hm*-pheox **3**.

As we mentioned in our pervious report,[9] the solubility of the catalyst in water using hydrophilic pendant was an essential factor in this biphasic catalytic reaction medium. Thus, we synthesized the insoluble catalyst **2** to compare its catalytic activity with the water-soluble catalyst **3**. Both catalysts **2** and **3** were synthesized as reported in our previous papers.[9,10] Fig. 1 shows The X-ray crystal structure of catalyst **2**[11] and Fig. 2 Shows the difference in the solubility of catalysts **2** and **3** in water-phase.



1 = $R^1 = CH_2OH$, $R^2 = Ph$, $R^3 = H$
2 = $R^1 = H$, $R^2 = R^3 = CH_3$
3 = $R^1 = CH_2OH$, $R^2 = R^3 = CH_3$

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0040-4039/

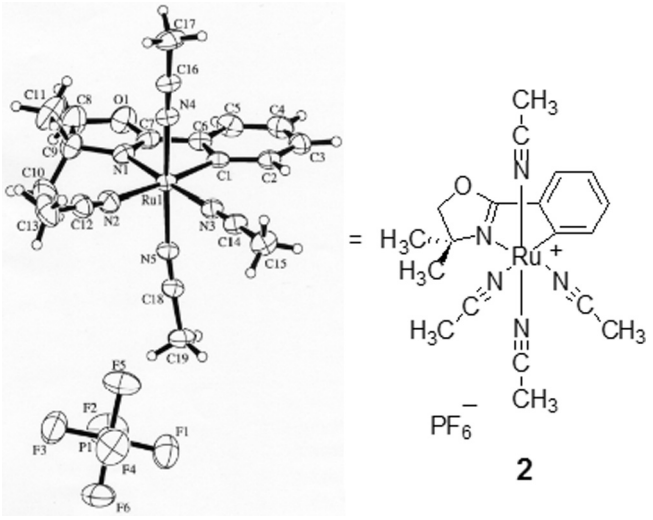


Fig. 1. The X-ray crystal structure of catalyst **2**.

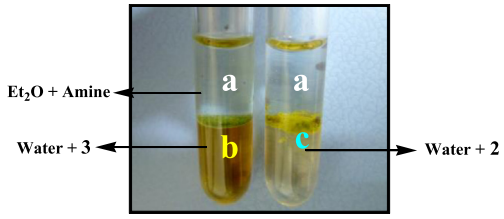


Fig. 2. (a) Ether phase contains amine substrates. (b) Catalyst **3** is completely soluble in water. (c) catalyst **2** is poor soluble in water.

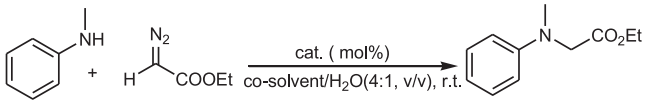
Initially, we evaluated the catalytic activity of catalysts **2** and **3** in NH insertion of EDA into *N*-methylaniline in DCM/water or ether/water biphasic medium and using different catalyst loading as shown in Table 1 (entries, 1–8). As expected, the catalyst **2** was so sluggish and delivered the product **5a** in low yield either with CH_2Cl_2 or with Et_2O (Table 1, entry 1 and 3) and the reason of this lower reactivity of catalyst **2** is attributed to the poor solubility of the catalyst in water phase as shown in Fig. 2.

On the other hand, the water-soluble Ru(II)-*hm*-pheox catalyst **3** showed excellent reactivity and delivered the product **5a** in >99% yield with catalyst loading 2.5 mol% in Et_2O/water phase (Table 1, entry 7). Remarkable yield (95%, Table 1, entry 2) was obtained when using CH_2Cl_2 with water. Other catalyst **3** loading lower or higher than 2.5 mol% showed lower yields (Table 1, entries 4–6 and 8). Significant decrease in reactivity was detected by using Toluene/water medium (Table 1, entry 9).

In addition, when using miscible organic solvents with water as CH_3CN, THF, and *i*-PrOH, good yields were obtained (Table 1, entries 10–12) but the obstacle of catalyst re-covering was still there. When using water only as the solvent, 23% yield was obtained (Table 1, entry 13).

The suggested mechanism for NH insertion of EDA into amine catalyzed by water-soluble catalyst **3** was shown in Scheme 1. Where EDA join with Ru(II)-*hm*-pheox **3** at the interface with evolution of N_2 gas. Amine attack the carbene carbon to deliver the next intermediate at interface which subsequently afforded the amino ester product in ether phase and the catalyst return back to the water phase. Hydrogen transfer occurred to deliver the aminoester derivatives in Excellent yield. Under the optimized reaction conditions (cat.**3** = 2.5 mol%, Et_2O/H_2O 4:1 v/v, biphasic medium at room temperature), we studied the NH insertion of EDA into a wide variety of amines as shown in Table 2. EDA was easily inserted into *N*-methyl aniline **3a** and delivered the *N*-substituted glycinate esters **5a** and **5b** in quantitative yields (Table 2,

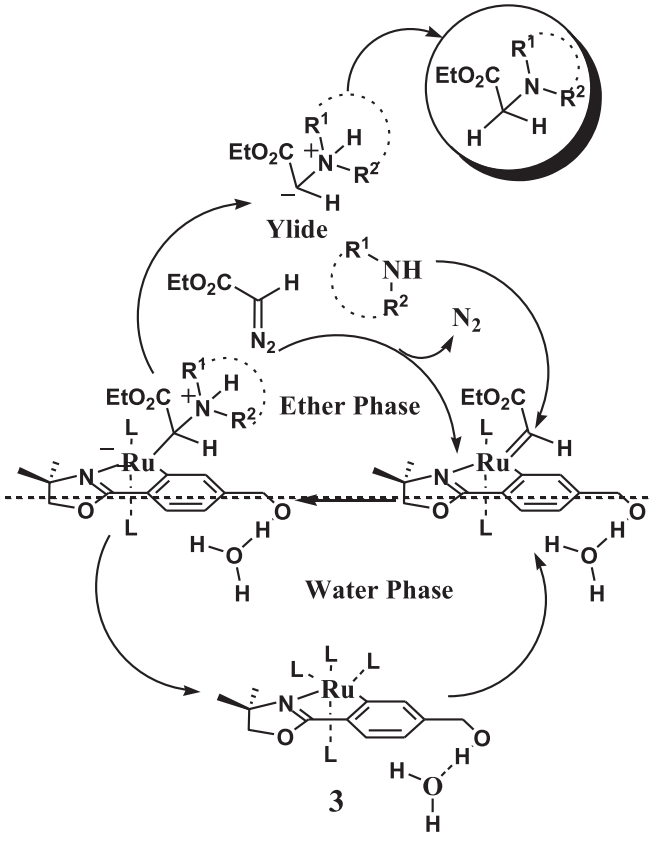
Table 1
Optimization of reaction conditions of NH insertion of EDA into *N*-methylaniline.[a]



3a 4 5a

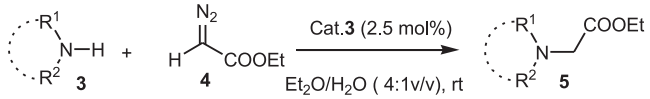
Entry	Co-solvent	Cat. (mol%)	Time (h)	**5a** Yield (%)[b]
1	CH_2Cl_2	**2** (2.5)	24	38
2	CH_2Cl_2	**3** (2.5)	2.0	95
3	Et_2O	**2** (2.5)	24	40
4	Et_2O	**3** (0.01)	5.0	43
5	Et_2O	**3** (0.5)	2.0	80
6	Et_2O	**3** (1.0)	2.0	91
7	Et_2O	**3** (2.5)	2.0	>99
8	Et_2O	**3** (3.0)	2.0	96
9	Toluene	**3** (2.5)	2.0	70
10[c]	CH_3CN	**3** (2.5)	2.0	85
11[c]	THF	**3** (2.5)	2.0	87
12[c]	*i*-PrOH	**3** (2.5)	2.0	92
13[c]	H_2O	**3** (2.5)	2.0	23

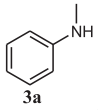
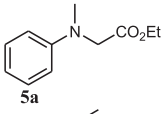
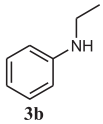
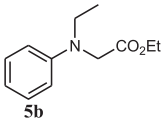
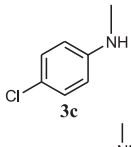
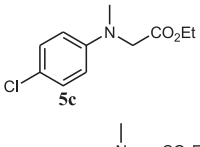
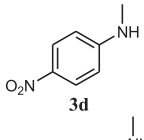
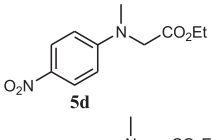
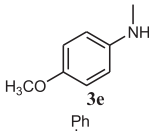
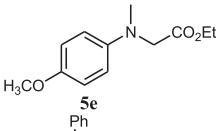
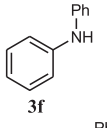
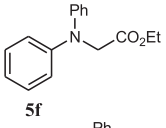
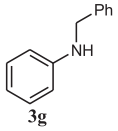
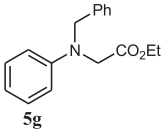
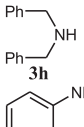
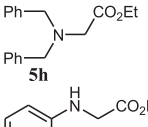
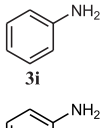
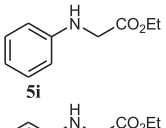
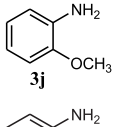
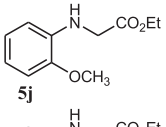
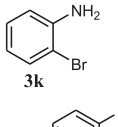
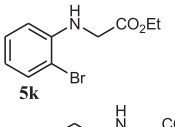
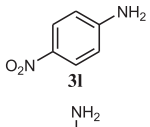
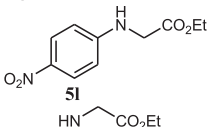
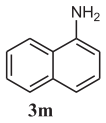
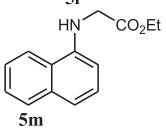
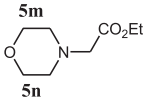
[a] Reaction conditions: A solution of *N*-methylaniline **3a** (0.3 mmol in 4.0 mL solvent) was added to a solution of Ru(II)-catalysts (mol%) in water (1.0 mL), then EDA **4** (0.3 mmol) was injected and the biphasic reaction mixture was stirred at room temperature.
[b] **5a** Yield of isolated product.
[c] The reaction is one phase medium.



Scheme 1. Suggested mechanism for NH-insertion of EDA into various amines catalyzed by **3** in a water/ether medium.

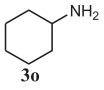
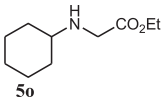
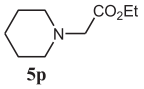
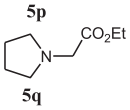
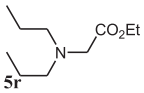
Table 2
NH insertion of EDA into various amine derivatives catalyzed by **3**.[a]



Entry	3	5	Time (h)	Yield (%)[b]
1	 **3a**	 **5a**	2.0	>99
2	 **3b**	 **5b**	2.5	>99
3	 **3c**	 **5c**	1.6	93
4	 **3d**	 **5d**	3.0	75
5	 **3e**	 **5e**	2.5	95
6	 **3f**	 **5f**	3.0	72
7	 **3g**	 **5g**	3.0	84
8	 **3h**	 **5h**	0.7	98
9	 **3i**	 **5i**	3.0	90
10	 **3j**	 **5j**	3.5	82
11	 **3k**	 **5k**	4.0	76
12	 **3l**	 **5l**	4.0	94
13	 **3m**	 **5m**	3.5	91
14	 **3n**	 **5n**	0.75	85

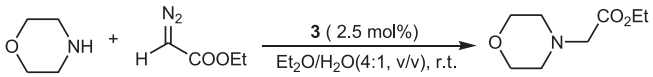
(*continued on next page*)

Table 2 (*continued*)

Entry	3	5	Time (h)	Yield (%)[b]
15	 3o	 5o	1.0	88
16	 3p	 5p	2.0	92
17	 3q	 5q	2.0	90
18	 3r	 5r	1.0	89

[a] Reaction conditions: A solution of amine **3** (0.3 mmol in 4.0 mL Et_2O) was added to a solution of Cat. **3** (4.61 mg, 0.0075 mmol, 2.5 mol%) in water (1.0 mL), then EDA **4** (0.3 mmol) was injected and the biphasic reaction mixture was stirred at room temperature.
[b] Yield of isolated product.

Table 3
Reusability of catalyst **3** in NH insertion of EDA into morpholine.[a]



3n 4 5n

Cycle	1	2	3	4	5	6	7	8
Yield (%)[b]	85	86	85	84	88	87	85	85

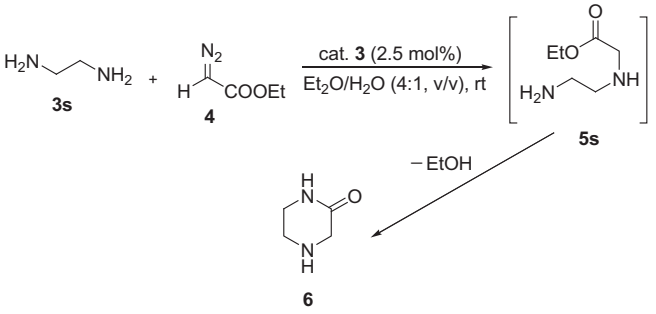
[a] Reaction conditions: A solution of morpholine **3n** (26.14 mg, 0.3 mmol in 4.0 mL Et_2O) was added to a solution of catalyst **3** (4.61 mg, 0.0075 mmol, 2.5 mol%) in water (1.0 mL), followed by injection of EDA **4**(0.3 mmol) at room temperature and the reaction was stirred for 1–3 h.
[b] Yield of isolated product.

entries 1 and 2) without formation of any dimers. It was found that the high electron withdrawing groups in the *para*-position of phenyl ring of *N*-methylaniline will reduce the insertion to give the product in 75% yield (Table 2, entry 4) while electron donating groups afforded excellent yields (Table 2, entry 3 and 5).

Additionally, as the bulkiness on nitrogen of the aromatic amine increased as the amino ester products decreased and vice versa (Table 2, entries 6, 7, and 8). In case of aniline, the mono- and di-ester product could be easily controlled by the addition of 1 or 2 equivalent of EDA. Aniline itself deliver very good yield compared with the *ortho*-substituents either withdrawing or donationg (Table 2, entries 9, 10, and 11). The *para*-substituted aniline is quite similar with aniline reactivity (Table 2, entry 12). Naphthylamine was as reactive as aniline and reacted with 1 equivalent of EDA to afford the corresponding product in 91% yield. More basic alicyclic primary and secondary amines such as morpholine, cyclohexyl amine, piperidine and pyrrolidine were also investigated and their amino ester products were obtained in very good yields in a short time (Table 2, entries 14, 15, 16, and 17). Dipropylamine was selected as an example of aliphatic secondary amine and delivered the insertion product in 89% yield (Table 2, entry 18).

Interestingly, the water-soluble Ru(II)-*dm*-Pheox (**3**) could be easily reused at least eight times without noticeable decrease in reactivity. Table 3 shows the reusability of catalyst **3** in the insertion of EDA into morpholine since the insertion product could be easily removed by decantation of the ether layer and the catalyst was washed 3 times with ether to be ready for the next cycle.

It is noteworthy that the synthesis of an intermediate of biological active compounds under very mild conditions and using water-soluble and reusable catalyst at room temperature is the target of numerous chemists. From this point of view we found that the water-soluble catalyst **3** could be catalyzed NH insertion of EDA into ethylene diamine **3s** to deliver intermediate **5s** which subsequently afforded 2-piperazinone **6** in 95% yield as shown in Scheme 2. The Piperazinone ring is considered as valuable scaffold for constructing common and wide array of biologically active molecules and natural products like (−)-Agelastatin A,[12–14] guaddinomine C_2,[15] and marcfortine B.[16] In addition, the piperazinone derivatives have been used as peptidomimetic for the discovery of bioactive molecules. Using our protocol we can reach to piperazinone by the easiest method in excellent yield and ability to reuse the catalyst several times compared with the previously reported strategies.[17]



3s 4 5s 6

Scheme 2. Synthesis of 2-piperazinone via NH-insertion of EDA into Ethylenediamine catalyzed by water-soluble catalyst **3** in biphasic ether-water medium.

In summary, a water-soluble Ru(II)-*hm*-pheox catalyst **3** was effectively catalyzed NH insertion of EDA into a wide array of primary and secondary amines, cyclic and acyclic in a biphasic water/ether medium and delivered biologically active precursors ethylglycinate ester derivatives in excellent yields. The products were obtained by simple decantation in a pure form without necessity for further purification in most cases and the water-soluble catalyst was readily recycled several times without significant decrease in reactivity. Additionally, the biological active piperazinone compound could be obtained in 95% yield from the insertion of EDA into ethylene diamine.

Typical procedure for NH insertion of EDA into various amine derivatives catalyzed by Ru(II)-*hm*-pheox 3

A solution of amine (0.3 mmol in 4.0 mL Et_2O) was added to a solution of Ru(II)-*hm*-pheox **3** (0.0075 mmol, 2.5 mol%) in water (1.0 mL), then EDA (0.3 mmol, 1.0 equiv.) was injected and the biphasic reaction mixture was stirred at room temperature. At the end of reaction, the ether layer was removed by decantation and the water-soluble catalyst was washed three times with ether (3×5.0 mL). The collected ether phase which contain the aminoester product was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The products in most cases were pure enough and there is no need for further purification. The water phase which contained the catalyst was recycled several times. The 2-piperazinone product **6** was purified by using column chromatography on silica gel (using CH_3OH only as eluent).

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2017.10.062.

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11. *X-ray analysis of catalyst* **2**: A single crystal ($0.15 \times 0.4 \times 0.7$ mm) was obtained by recrystallization from acetonitrile-toluene. Selected bond lengths [Å] and angles [°]: Ru1–N1 2.088(3); Ru1–N2 2.147(4); Ru1–N3 2.032(4); Ru1–C1 2.035(4); N1–Ru1–C1 79.4(2); N2–Ru1–C1 176.3(1); C1–C6–C7 112.5(4); Ru1–C1–C6 114.3(3). Cystallographic data of catalyst **2**: $C_{19}H_{24}F_6N_5OPRu$, monoclinic, space group $P2_1/c$ (#14), a = 8.254(2) Å, b = 22.940(2) Å, c = 13.281(1) Å, β = 94.06(1)°, V = 2508.4(6) Å^3, Z = 4, D_{calcd} = 1.548 g cm^{-1}, R (all data) = 0.037, Rw (all data) = 0.038, no. of dbsd rflcns 4421 ($I > 3\alpha$). Crystallographic data has been deposited in Cambridge Crystallographic Data Centre as supplementary data with CCDC-no. 648769. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/deposit.
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